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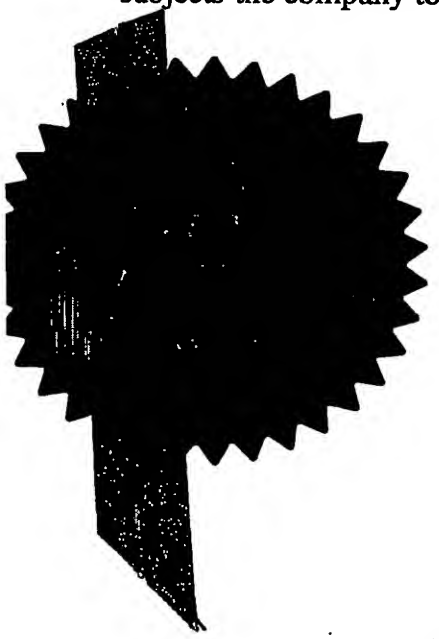

Signed P. Mahoney

Dated 20 June 2003

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Request for grant of a patent

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25 JUL 2002

The Patent Office
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1. Your reference — CBT/JD/P33086

2. Patent application number
(The Patent Office will fill in his part) — 0217336.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

473587003

United Kingdom

4. Title of the invention — Multicomponent pharmaceutical dosage form

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)*

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property CN925.1
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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c) any named applicant is a corporate body
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Request for preliminary examination and search *(Patents Form 9/77)*	1 ✓
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11. We request the grant of a patent on the basis of this application

Signature Clive Thompson Date 25-Jul-02

C B Thompson

12. Name and daytime telephone number of person to contact in the United Kingdom: Miriam Morris 020 8047 4445

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Pharmaceutical Dosage Form

The present invention relates to a pharmaceutical dosage form, being a multicomponent dosage form comprising components in the form of a body and a film means and being suitable for oral dosing.

Various types of pharmaceutical dosage form are known for oral dosing. Pharmaceutical capsules are well known, generally being intended for oral dosing. Such capsules generally comprise an envelope wall of a pharmaceutically acceptable, e.g. orally ingestible, polymer material such as gelatin, although other materials for capsule walls, e.g. starch and cellulose based polymers are also known. Such capsules generally have soft walls made by making a film on a capsule former, which is then allowed to dry. Rigid walled capsules made by injection moulding are also known, see for example US 4576284, US 4591475, US 4655840, US 4738724, US 4738817 and US 4790881 (all to Warner Lambert). These disclose specific constructions of capsules made of gelatin, starch and other polymers, and methods of making them by injection moulding of hydrophilic polymer – water mixtures. US 4576284 specifically discloses such capsules provided with a cap which closes the capsule, and which is formed in situ on the filled capsule by moulding. US 4738724 discloses a wide range of rigid capsule shapes and parts.

Multi-compartment capsules, including those of the type where each compartment has different drug release characteristics or for example contains a different drug substance or formulation are also known, for example in US 4738724 (Warner-Lambert), US 5672359 (University of Kentucky), US 5443461 (Alza Corp.),WO 9516438 (Cortecs Ltd.), WO 9012567 (Helminthology Inst.), DE-A-3727894, BE 900950 (Warner Lambert), FR 2524311, NL 7610038 (Tapanhony NV), FR 28646 (Pluripharm), US 3228789 (Glassman), US 3186910 (Glassman) among others. US 4738817 discloses a multicompartment capsule with a similar construction to those of US 3228789 and US 3186910, made of a water-plasticised gelatin.

Another type of dosage form is disclosed in WO 01/08666 (SmithKline Beecham) wherein the dosage form comprises two or more capsule shells linked together via a linker unit having a plug part which extends into an open end of a shell.

Whilst the dosage form of WO 01/08666 provides advantages over other prior art dosage forms e.g. greater flexibility in producing a dosage form adapted to a patient's specific requirements, there nevertheless remains a need for alternatives. In particular there remains a need for a dosage form that is of a simple construction, is easy to manufacture and that can provide a desired drug-release profile e.g constituting both immediate and delayed release of a drug substance in a single dosage form. In particular it is an object of this invention to provide a dosage form that is easier to fabricate using ultrasonic welding to connect the components together. In the dosage form of WO 01/08666, to form the ultrasonic weld it is normally necessary to transmit ultrasonic energy along the whole length of the capsule shell to weld it to the linker. This can result in problems of shattering of the capsule shell, the need for a high power ultrasonic horn and handling capacity. It is an object of the invention to provide a dosage form that meets these requirements.

According to the invention there is provided a multicomponent pharmaceutical dosage form suitable for retaining drug substance which drug substance can be released to provide a controlled drug release profile in the gastrointestinal environment, characterised by a body having at least one cavity, said cavity having a mouth opening, and a film means connected to the body and closing the mouth opening.

By "controlled drug release" is meant that drug may be released from the dosage form to provide a defined, pre-determined drug release profile. Drug may be released from the dosage form at different rates, at different times following administration to the patient, or in different sites within the patient's gastrointestinal system. For example ~~the dosage form may be designed to provide rapid release, immediate, modified~~ release such as sustained or pulsatile release characteristics e.g. an immediate first pulse of drug followed by a delayed second pulse of drug at some later time point. Preferably the dosage form provides a pulsed release profile resulting in immediate release of a portion of the drug substance contained therein, typically up to 15 minutes following ingestion of the dosage form, followed by a subsequent or delayed release of another portion of drug contained in the same dosage form, effected at some later point, typically up to 4 hours later. Usually immediate release takes place in the

region of the stomach whilst delayed release occurs in another part of the gastro-intestinal compartment such as the small intestine or the gut.

Suitably the dosage form opens to release drug substance in the gastro-intestinal environment. The process by which the dosage form opens may comprise one or more physical and/or chemical processes. For example the film means, the body, or a connection between the two such as a weld, may on exposure to a particular gastrointestinal environment and/or after a suitable time delay, shear or burst to release the content of a part or all of the dosage form. Alternatively a component of the dosage form e.g. the film means, the body, a connection between the two, may dissolve partly or wholly or be otherwise breached to release the content of part or all of the dosage form.

Suitably the invention may comprise a plurality of cavities and/or a plurality of film means. In a first embodiment of the invention the body comprises a first cavity and a second cavity, the first and second cavities having a respective first and a second mouth opening, and a first and second film means connected to the body and closing the first and second mouth openings.

Suitably in this embodiment the body may be shaped so as to define a first and second cavity therein. More particularly the body may comprise a base wall having an upper and a lower surface, the first cavity being defined by a first skirt wall extending upwardly (hereinafter referred to as an 'upward' direction) away from the upper surface of the base wall to terminate in a rim defining the first mouth opening, the second cavity being defined by a second skirt wall extending downwardly (hereinafter referred to as a 'downward' direction) away from the lower surface of the base wall to terminate in a rim defining the second mouth opening. In such an embodiment the body may be generally 'H'shaped in longitudinal section with the first and second cavities formed in the two opposing hollows between the horizontal linker portion of the 'H' and the side arms of the 'H'. By "generally 'H'"shaped is also intended to encompass other like shaped body configurations that give rise to a cavity or cavities either side of a linker portion e.g. a body comprising a flattened 'H' shape in section wherein the length of the arms of the 'H' is equal to or shorter than the width of the

linker portion between the arms. The term 'H' shaped includes shapes with parallel, curved, convergent or divergent arms. Suitably the ratio of the length of the skirt walls: width of the base walls is in the range 3:1 to 1:5. Suitably the first and second film means are connected to an upper and lower rim, respectively, of the skirt walls.

Suitably the film means is connected to the respective rims of each mouth opening and serve to close the mouth openings thereby sealing each cavity enabling drug substance and any other desired material, e.g. a pharmaceutically acceptable carrier, to be retained therein.

The first and/or second film means may form a blister convex relative to the respective first and/or second cavity. The first/and or second film means may form a substantially planar surface relative to the first and second cavity. Preferably the film means is substantially planar and may be connected to a correspondingly substantially planar portion of the body, thereby facilitating a good seal between the component parts.

In a second embodiment the body may comprise a base closed by a base wall having an upper surface, the first and second cavities being adjacent and defined by skirt walls extending upward from the upper surface of the base wall, the skirt walls terminating in a common rim defining the respective first and second mouth openings. Suitably the adjacent first and second cavities and their mouth openings are divided from each other by a dividing wall across the base wall and connected to the common skirt wall. Preferably the base wall is generally flat and the skirt wall and the dividing wall extend generally perpendicular to the upper surface of the base wall. A first and second film means may connect to the body to close both the first and second mouth openings of the first and second cavities respectively. Suitably the first and second film means are connected to the rim of the mouth openings.

In an alternative second embodiment comprising a first body and optionally second body, a first film means may close the mouth opening of the first cavity and the second cavity may be closed by a second film means or a second body connected to the first body. Suitably the first film means may be connected to the rim of the

mouth opening of the first cavity and second film means or the second body (when present) may connect to an exterior skirt wall extending upwards from the upper surface of the base wall of the first body.

In a variant of the second embodiment the base wall may comprise a weakened portion such that release of drug substance contained in a first cavity in the vicinity of the weakened portion may be released in advance of drug being released from a second cavity which does not contain a base comprising a weakened portion. Advantageously the second embodiment allows drug to be filled in the dosage form in a single step operation.

In a third embodiment the body defines a cavity having a longitudinal depth direction and the film means comprises a first and second film means, longitudinally spaced apart so as to define at least one other cavity. Suitably the dosage form is substantially tub-shaped. For example the dosage form may comprise a body having a base wall having an upper surface and a skirt wall extending longitudinally upwardly therefrom to terminate in a rim defining the mouth opening. In this embodiment one cavity is generally located above the other. For example the mouth opening may be closed by a first film means and a second film means may be located under the said first film means to define an upper compartment between the first film means and the second film means. For example both the first and second film means may be connected to the rim of the skirt wall in the same vicinity. For example the first film means may be on top of the second film means, in contact with the second film means and connected to the second film means. Alternatively for example the first film means may be connected to the rim of the skirt wall whilst the second film means is longitudinally downwardly remote from the first film means e.g. the second film means may be connected to the skirt wall intermediate between the rim and the base wall so that the second film means is intermediate between the first film means and the base wall e.g. less than 50% of the depth or more than 50 % of the depth down. In the third embodiment the first film means may be substantially planar or blister convex relative to the second film means. The skirt wall may further comprise a ledge to accommodate the first and/or second film means. For example if the second film means is connected to the skirt wall intermediate between the first film

means and the base wall a ledge may be provided intermediate between the first film means and the rim and the base wall.

In an alternative dosage form there is provided a first body comprising a first cavity having a mouth opening and a second body comprising a second cavity having a mouth opening which bodies are connected to each other around respective rims of each mouth opening and a film means separates the first cavity from the second cavity. Suitably the first and second body may be arranged mouth-to-mouth i.e. one mouth facing upwardly and the other facing downwardly. A single film means may close both mouth openings or each mouth opening may be closed by a respective film means. Suitably each cavity contains drug substance as hereinbefore described. In one embodiment the film means and one body may comprise material to effect delayed release and the other body may comprise material to effect immediate release. An embodiment such as this provides a dosage form having modified release characteristics.

Advantageously the invention may provide a dosage form in a desired shape. For example the dosage form may be substantially cylindrical, which includes shapes which have a circular, oval or oblate circular cross section across the longitudinal axis, and shapes which have parallel or tapering e.g. with side walls which taper conically, which includes both true cones i.e. with straight side walls, and cones with curved side walls, over at least part of their extent. Dosage forms that are substantially elongated or circular when viewed in cross section across the longitudinal axis but being short in their longitudinal direction relative to their dimension across the cross section ~~may resemble respectively capsules or tablets.~~ Dosage forms that resemble tablets are preferred.

Film means of the invention may be produced in a number of ways e.g. by hot-melt extrusion, solvent casting, or by an injection moulding process to produce, respectively, a continuous sheet / layer, or a series of discrete film parts. Preferably the film means is in the form of a sheet / layer that may be cut to size to fit the corresponding body. Film means may also be combined to form multi-laminated constructions in which different polymer films are joined to create a sandwich-type

layer with increased functionality compared to single layer films. Suitably the relative thickness of the film means to that of the base wall of the body is in the range 1:100 preferably 1:50, even more preferably 1:10 or 1:5.

A body according to the invention may be produced by injection moulding processes which can enable the body to be made with precision. Suitable techniques of injection moulding are known for example from the art of manufacture of small plastic components e.g. small parts of LEGO toys. Processes such as those described in Cuff. G and Raouf. F, Pharmaceutical Technology, June 1998, p96-106, may be used to manufacture body parts. Consequently the invention also provides a moulding process for example an injection moulding or powder compression process wherein the body parts of the dosage form are made in respective mould cavities. The invention also provides a mould or die, suitable for use in the moulding process. Such a mould or die may have a mould cavity corresponding to the shape of the body. Moulds may be made by known metal engraving processes such as spark erosion and it is generally preferred to use moulds made from pharmaceutically acceptable metals e.g. steels of the type known for use in tablet compression dyes.

In an assembled dosage form of the invention, the component parts of the dosage form namely the film means and the body may be connected together e.g. by a weld such as a thermal weld, an ultrasonic weld, inductive weld or an adhesive weld (e.g. curable adhesives such as UV curable adhesive). A thermal weld may for example be achieved by bringing the film means and the body into adjacent contact and applying localised heating for example produced by directing a laser beam or a fine jet of hot gas e.g. nitrogen at the area where the film means and the body are in contact. In thermal, inductive and ultrasonic welding normally localised fusion together of the materials of adjacent parts of the dosage form which are in contact occurs, and on subsequent solidification of the materials a bond is formed between the adjacent parts. An adhesive weld may be achieved by applying an adhesive (e.g. curable adhesives such as UV curable adhesive) to parts of the dosage form which when the dosage form is assembled are in contact, and then causing or allowing the adhesive to set.

The multicomponent dosage form of the present invention is particularly suited to fabrication using ultrasonic welding. Ultrasonic welding is a known technique involving the use of high frequency sound energy to soften or melt a thermoplastic material at the site where a joint with the material is required. A general description of ultrasonic welding is for example to be found in the publication "Ultrasonic Welding of Thermoplastics" (TWI Ltd., Abington, Cambridgeshire GB, (1997)). Parts to be joined are held together under pressure and then subjected to ultrasonic vibrations usually at a frequency of 20 – 40 kHz. The actual mechanism responsible for the generation of heat at the joint site is not well understood. An ultrasonic welding machine comprises five main components, being a power supply, a control system, a welding head, fixturing to hold the parts to be welded, and a system to apply the required pressure. The power supply converts electricity into high frequency electric power which drives a transducer, e.g. a piezoelectric transducer, which converts electrical energy, e.g. from the mains supply, into mechanical, i.e. ultrasonic, energy. Between the transducer and the parts to be welded is located a booster and horn system, being a usually metallic component which serves to amplify the ultrasonic waves (the booster horn), transmit the clamping pressure, and deliver the sound energy to the part to be welded (the sonotrode or welding horn). For successful ultrasonic welding careful design of the parts to be welded and set up of the welding equipment is important. The rim of the mouth opening may be profiled to facilitate formation of an ultrasonic weld.

One suitable profile of the rim of the mouth opening to facilitate ultrasonic welding of the film means thereto may comprise a rim in the form of an upwardly facing generally flat surface generally perpendicular to the depth direction of the cavity. Optionally such a surface may be bounded by a kerb edge e.g. a small upwardly extending wall around the outer periphery of the rim. A preferred profile comprises one or more small upwardly extending ridges on such a surface. The film means may be placed on top of such a ridge and in contact with it, and by applying the ultrasonic horn to the film means on the opposite side of the ridge, the ridge can be caused to collapse and form the weld. Additionally or alternatively the rim may have a concavity such as a groove therein into which the film means e.g. an edge thereof,

may fit. Alternatively the rim may be flat and the ultrasonic horn may have one or more small upwardly extending ridges on the surface acting on the film in order to focus sound energy on a specific point or points to achieve welding of the two components.

The film means and body of a dosage form of the invention are made of materials having particular physico-chemical characteristics to achieve a desired release profile. The film means and the body may be comprised of material designed to provide rapid dissolution, immediate dissolution and/or modified dissolution e.g. to confer sustained or pulsatile release characteristics, and combinations thereof. For example in an embodiment according to the invention e.g. in the first embodiment herein described, the first film means may be designed to provide rapid or immediate dissolution and the second film means may provide modified dissolution such as sustained or pulsatile release characteristics. In an alternative arrangement of the first embodiment the first film means may be designed to provide rapid or immediate dissolution and the body may be designed to provide modified dissolution. In an alternative embodiment, such as a variant of the second embodiment, the film means may be designed to provide modified dissolution and the body, e.g. in the vicinity of the weakened portion may provide rapid or immediate dissolution.

Suitable materials for the provision of a desired release profile include pharmaceutically acceptable polymeric blends which may be injection moulded to form a body and may also be made into thin films to provide the film means of the dosage form.

For purposes herein representative examples of polymers suitable for injection molding or film-formation into multicomponent dosage forms and for use in pharmaceutical applications, include, but are not limited to, poly(ethylene) oxides (PEO), polyethylene glycol's (PEG), mixtures of PEG's and PEO's, polyvinyl alcohol (PVA), polyvinyl acetate, povidone (polyvinyl pyrrolidone), cellulose derivatives such as carboxymethyl cellulose, methyl cellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropylcellulose, hydroxyethyl methylcellulose, hydroxypropylmethyl cellulose (HPMC), hydroxypropylmethyl cellulose phthalate,

cellulose acetate phthalate, noncrystalline cellulose, starch and its derivatives such as hydroxyethyl starch, sodium starch glycolate, natural polymers (such as polysaccharides like pullulan, carrageenan, xanthan, chitosan or agar gums), polyacrylates and poly (meth)acrylates, and its derivatives such as the Eudragit family of polymers available from Roehm Pharma, poly(alpha-hydroxy acids) and its copolymers such poly(caprolactone), poly(lactide-co-glycolide), poly(alpha-aminoacids) and its copolymers, polyglycolysed glycerides (such as Gelucire® 44/14, Gelucire® 50/02, Gelucire® 50/13 and Gelucire® 53/10), carboxyvinyl polymers (such as Carbopols), and polyoxyethylene-polyoxypropylene copolymers (such as Poloxamer 188™); and combinations or mixtures thereof.

Also potentially suitable for use herein are the polymers poly(orthoesters), polyphosphazenes, poly(phosphoesters), and polyanhydrides, and combinations or mixtures thereof.

Additionally, hyaluronic acid, alginates, carragenen, collagen, gelatin, and albumen may also be suitable for injection moulding herein, either alone or in combination with another polymeric blend. It is recognised that the ultimate choice of polymers if not previously approved by the regulatory agencies of the world, are in the category of generally recognized as safe (GRAS) approved.

Especially suitable polymers for use in the invention are those that preferentially dissolve or disintegrate at different points in the digestive tract and include the known acrylic and/or methacrylic acid-based polymers which are soluble in intestinal fluids e.g. the Eudragit series of polymers, produced by Roehm GmbH in Germany. Examples of Eudragit polymers include Eudragit E e.g. Eudragit E100, which preferentially dissolve in an acidic, e.g. up to pH 5, environment e.g. in the acidic environment of the stomach, or enteric polymers such as Eudragit L and/or Eudragit S, which preferentially dissolves in a more alkaline pH environment e.g. in the environment of the intestine. Other suitable polymers also include polymers which are insoluble but hydrate at a controlled rate e.g. at a predetermined rate in the digestive tract such as Eudragit RL e.g. Eudragit RL 100 and/or Eudragit RS e.g. Eudragit R100 and/or blends of Eudragit polymers.

The group of poly(meth)acrylate copolymers, such as Eudragit 4135F and Eudragit E100 are a preferred polymer for use in this invention. Eudragit 4135F comprises a methacrylic acid, methylmethacrylate, methyl acrylate copolymer in a typical ratio 25:65:10 with a dissolution threshold of pH greater than 7.2. Eudragit E100 comprises butylmethacylat-(2-dimethylaminoethyl)methacrylat-methylmethacylat-copolymer (1:2:1) and is a copoloymer based on (2-dimethylaminoethyl)methacrylalate, butyl methacrylate and methylmethacrylate, typically in a 2:1:1 ratio, having a mean molecular weight of about 150,000. It contains not less than 20.8 and not more than 25.5% dimethylaminoethyl groups in the dry substance. Another polymer disclosed in US 5,705,189, Emulsion E2 (column 6 line 10), a copolymer of methacrylic acid, methyl methacrylate and methyl acrylate, suitably in a ratio of 10:25:65, is a preferred polymer for use in the present invention, as are the polymers disclosed in WO 01/43935 and WO 01/39751, both in the name of Roehm.

Suitably a delayed release or pulsed release body or film means comprises Eudragit 4135F. Suitably an immediate release body or film means comprises Eudragit E100. Eudragit E100, for immediate release, and Eudragit E4135F, for delayed or pulsed release, may be used in any film means/body combination. For example a dosage form of the invention comprising a film means and a body may comprise an immediate release first film means and a delayed release second film means comprising E4135F and E100 respectively and a delayed release body that may comprise E100.

When the polymer comprises Eudragit 4135F, at least one lubricant and one dissolution modifying agent is also used to achieve quality, non-distortion molded components which readily release from injection molds. Suitably the polymer is used in an amount of about 20 to about 90% w/w , preferably from about 50 to 90%w/w, the dissolution modifying excipient e.g. a surfactant is used in an amount of about 2.5 to about 30% w/w, and the lubricant in an amount up to 30%w/w. Preferably the polymeric blend further comprises a plasticizer in a range from 0% to about 10%w/w and a processing agent in a range from 0% to about 10%w/w. A suitable polymer blend comprises a lubricant e.g. stearyl alcohol ca. 12%, a surfactant e.g. sodium

dodecyl sulphate ca. 1%, a processing/swelling aid e.g. hydroxypropylmethylcellulose ca.5%, a swelling aid e.g. croscarmellose sodium ca.10% and sodium starch glycollate ca. 10% and a polymer e.g. Eudragit 4135F up to 100%.

When the polymer comprises Eudragit E100, the polymeric blend may further comprise a dissolution modifying agent and a lubricant. Suitably the polymer is used in an amount of about 30 to about 90% w/w, the dissolution modifying excipient is used in an amount of about of about 5 to about 70%w/w, and the lubricant is used in an amount up to about 30%w/w. Preferably the polymeric blend further comprises a plasticizer in the range from 0% to about 5% and a processing agent in the range 0 to 10%w/w. A suitable polymer blend comprises a lubricant e.g. stearyl alcohol ca. 12%, a processing aid e.g. polyethylene oxide ca. 20%, a strengthening aid e.g. talc ca. 10% and co-povidone ca. 5% and a polymer e.g. Eudragit E100 ca 53%.

In general, for use herein, suitable dissolution modifying excipients include a disintegrant such as sodium starch glycollate e.g. Explotab, cross-linked PVP e.g. Kollidon–CL, copovidone e.g. Kollidon VA 64 or starch e.g. starch 1500; a swelling agent such as polyvinylpyrrolidone (PVP, also known as povidone) e.g. ISP-plasdone or BASF-Kollidon and primarily grades with lower K values e.g. K-15, K25 and K-30; a cellulosic derivative such as hydroxypropylmethylcellulose; a wicking agent such as a low molecular weight solute e.g. mannitol, lactose and starch; inorganic salts such as sodium chloride (typically at 5-10%). Suitable lubricants or glidants include stearyl alcohol, steraric acid, glycerol monosterate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, fumed silica and combinations thereof. Suitable plasticizers include triethyl citrate (TEC), triacetin, tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; and combinations or mixtures thereof. The choice of polymer will determine which plasticizer is suitable for use and this will be apparent to the man skilled in the art. For instance, triacetin is not preferred for use with E100 or 4135F at levels of about 5% but may be suitable for use with Eudragit RS or RL, or PVA.

The dosage form is particularly suitable for presentation as an oral dosage form containing one or more drug substances e.g. containing a combination of drug substances. When there is more than one cavity present each cavity may contain the same or different drug substance which may be released at the same time or a different rate or time after administration or place in the patient's gastro-intestinal system. Advantageously the invention provides a dosage form having variable drug content and/or drug release characteristics to provide a dosage form tailored to specific administration requirements. The drug substance(s) contained in the cavity(ies) may be present in any suitable form e.g. in the form of powder, pellets, granules, semisolids or liquids.

Dosage forms of the invention may be prepared by various processes. A typical process for making a dosage form comprising two cavities comprises the following steps:

1. Forming a body e.g. by injection moulding of a suitable polymer and forming a film means e.g. hot-melt extrusion
2. Filling a first cavity with drug substance
3. Closing the first cavity with a film means
4. Filling a second cavity with the same or different drug substance
5. Closing the second cavity.

When the dosage form comprises a body having two oppositely facing i.e. upwardly and downwardly facing mouth openings it is preferred to perform steps 2 and 3 on the cavity which is facing upwardly then to invert the body so the other cavity is facing upwards, then perform steps 4 and 5.

Details of the dosage forms referred to above will now be described with reference to Figs.1-9 which show longitudinal plans and perpendicular views of a dosage form of the invention.

Referring to Fig. 1 a dosage form is shown having an body 11, 'H'-shaped in longitudinal section comprising a first cavity 12 and a second cavity 13, the first and second cavities having a first and second mouth opening, 14 and 15, respectively.

The first and second mouth openings 14 and 15 are closed by first and second film means 16 and 17 respectively connected by an ultrasonic weld to the respective rim 18, 19 of the mouth opening 14, 15. The first and second film means 16 and 17 form a blister convex relative to the respective first and second cavity. The first film means 16 may comprise material that confers delayed release characteristics upon the dosage form e.g. Eudragit 4135F, whilst the second film means 17 may comprise material that confers immediate release e.g. Eudragit E100. The body comprises a base wall 110 and skirt walls 111,112 extending respectively upwardly and downwardly from the base wall 18 to define the cavities 12,13. The cavities 12 and 13 contain drug substance (not shown) and, if desired, any pharmaceutically acceptable carrier.

Referring to Fig. 2 a dosage form is shown comprising a body 21, generally 'w' shaped in cross section having a base wall 22 having an upper surface 23 with a first and second cavity, 24 and 25, being defined by a skirt wall 26 extending from the upper surface 23 and terminating in a common rim 29 defining a first and second mouth opening 28 and 29. A first and second film means, 210 and 211, which are generally planar seal the first and second mouth openings 28 and 29. The first and second cavities 24 and 25 are divided from each other by a dividing wall 212 across the base wall 22. The first and second film means 211 and 212 and may comprise material that confers immediate release and the body may comprise material that confers delayed release. A single common film (210,211) may close both mouth openings 28,29.

Referring to Fig 2A a variation of the dosage form of Fig. 2 is shown, and corresponding parts are numbered correspondingly. A second body 213 is connected to a first body 21.

Referring to Fig. 3 a dosage form is shown disclosing a variant of the dosage of Fig. 2 in which the base wall 22 comprises a weakened portion 31 in the form of a thinned region of the base wall 22.. The weakened portion 31 may comprise an immediate release material and the film means 211 and 212 may comprise a delayed release material.

Fig. 4 shows the dosage form of Figs. 2 and 3 in plan, without the film means. The shape and position of thinned region 31 is also shown dotted.

Referring to Fig.5 there is disclosed a dosage form comprising a generally 'U'-sectioned shaped body 51 in cross section having a first cavity 52. A first film means 53 closes the first cavity 52 at the rim 54 of a skirt wall 5 extending upwardly from the base wall 56 of the body 51. A second film means 57, located above the first film means 53 defines a second cavity 58. Both cavities 52 and 58 contain drug substance (not shown). The first film means 53 may form a planar or concave blister relative to the substantially planar base wall 56. The second film means 57 may form a planar or convex blister (as shown) relative to the substantially planar base wall 56. Second film means 57 is situated above and in contact with first film means 53 and is connected thereto.

Referring to Fig. 6 a dosage form is shown disclosing a variant of the dosage form of Fig. 5. In this embodiment the first film means 61, is located between the second film means 62 and the base wall 63 of the body 64. The body 64 has a ledge 65 which extends inwardly from the skirt wall 66 and which serves as a means for supporting and providing a connecting point between the first film means 61 and the body 64. First and second cavities 67,68 are thereby defined.

Referring to Fig. 7 a dosage form is shown comprising a first body 71 having a first cavity 72 having a mouth opening 73 and a second body 74 comprising a second cavity 75 having a mouth opening 76. The bodies 71, 74 are connected to each other around the respective rims 77 and 78 of skirt walls 79 and 710, extending respectively upwardly and downwardly from base walls 711, 712, of the first and second bodies 71 and 74 at weld 713. A film means 714 is welded at 715 to a rim edge of body 71 to close mouth opening 73. Each cavity 72 and 75 contain drug substance (not shown). The first body 71 may comprise immediate release material and the second body 74 and the film means 714 may comprise delayed release material.

Fig. 8 shows a construction of the rim 18 of a dosage form according to Fig.1, suitable for forming an ultrasonic weld. The rim 18 comprises a generally flat upwardly

facing surface region 181, bounded at its outer periphery by a small upstanding kerb 182. The inner periphery of the region 181 is bounded by a small upstanding ridge 183, although the ridge 183 can be at other positions between the inner and outer periphery. A film means 16 is located on the ridge 183 and retained by the kerb 182, and an ultrasonic welding horn (not shown) can be applied at the point illustrated by the arrow in Fig. 8 to cause the ridge to collapse and form a weld between the film means 16 and the region 181.

Fig. 9 shows a perspective view of a dosage form according to Fig.1.

Claims

1. A multi-component pharmaceutical dosage form suitable for retaining drug substance which drug substance can be released to provide a controlled drug release profile in the gastrointestinal environment, characterised by a body having at least one cavity said cavity having a mouth opening and a film means connected to the body and closing the mouth opening.

2. A multi-component pharmaceutical dosage form according to claim 1 wherein body and /or the film means is made of materials such that the dosage form opens to release the drug substance in the GI environment.

3. A multi-component pharmaceutical dosage form according to claim 1 or claim 2 wherein the film means is connected to the body by a weld.

4. A multi-component pharmaceutical dosage form according to claim 3 wherein the weld is an ultrasonic weld.

5. A multi-component pharmaceutical dosage form according to any one of claims 1 to 4 wherein the body comprises a first cavity and a second cavity therein, the first and second cavities having a first and a second mouth opening respectively, and a first and second film means connected to the body and closing the first and second mouth openings.

6. A multi-component pharmaceutical dosage form according to claim 5 wherein the body comprises a base wall having an upper surface, the first cavity is defined by a skirt wall extending away from the upper surface of the said base wall to terminate in a rim defining the first mouth opening, the second cavity is defined by a skirt wall extending away from the lower surface of said base wall to terminate in a rim defining the second mouth opening.

7. A multi-component pharmaceutical dosage form according to claim 6 wherein the first and/or second film means is a blister convex relative to the respective first and/or second cavity.

8. A multi-component pharmaceutical dosage form according to claim 6 wherein the first and/or second film means is substantially planar relative to the first and/or second cavity.

9. A multi-component pharmaceutical dosage form according to any one of claims 1 to 5 wherein the body comprises a base wall having an upper surface, both the first and second cavities are defined by adjacent skirt walls extending from the upper surface of the said base wall to terminate in a rim defining the respective first and second mouth openings, the first and second film means connected to the body close both the first and second mouth openings.

10. A multi-component pharmaceutical dosage form according to claim 9 wherein the first and second cavities are adjacent and are divided from each other by a common skirt wall and the rims of their mouth openings are substantially coplanar.

11. A multi-component pharmaceutical dosage form according to any one of claims 1 to 4 wherein the film means comprises a first and second spaced apart film means defining a compartment suitable for retaining drug substance between said first and second film means.

12. A multi-component pharmaceutical dosage form according to claim 11 wherein the body comprises a base wall and a skirt wall extending therefrom to terminate in a rim defining the mouth opening, the mouth opening being closed by a first film means and a second film means is located under the said first film means to define an upper compartment between the first film means and the second film means.

13. A multi-component pharmaceutical dosage form according to claim 11 wherein the body comprises a base wall and a skirt wall extending therefrom to terminate in a rim defining the mouth opening, the first mouth opening being closed by a first film means and a second film means intermediate between the said first film means and the base wall to defines a first compartment between the first film means and the second film means and a second compartment between the second film means and the base wall.

14. A multi-component pharmaceutical dosage form according to claim 13 wherein the skirt wall has an internal ledge to which the second film means is connected.

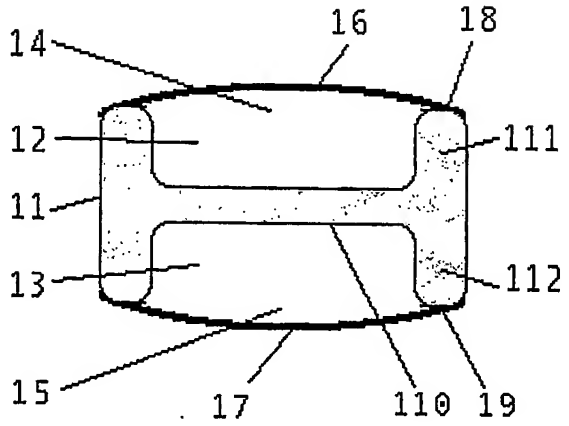

Fig 1

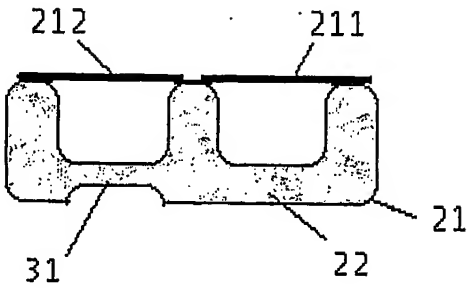

Fig 3

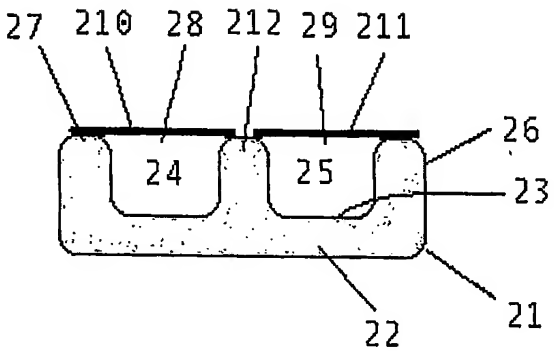

Fig 2

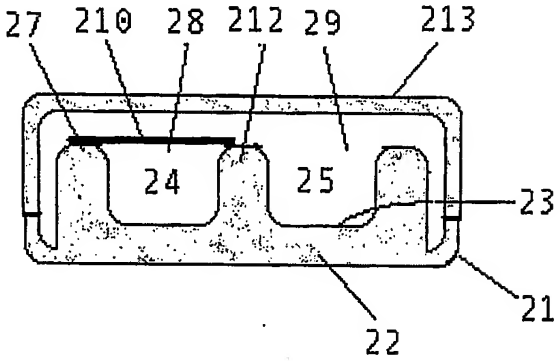

Fig.2A

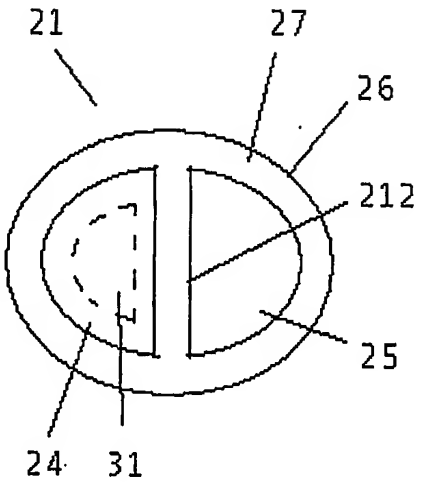

Fig 4

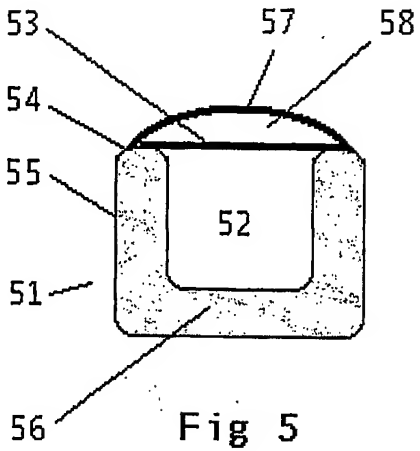

Fig 5

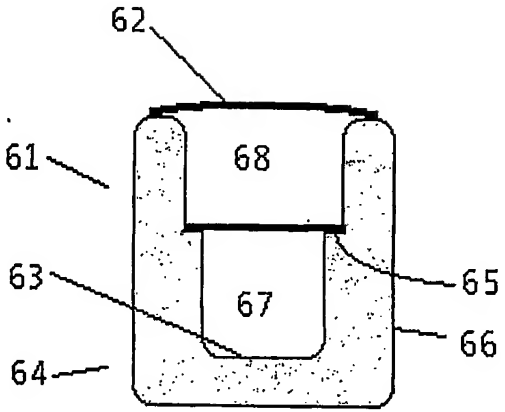

Fig 6

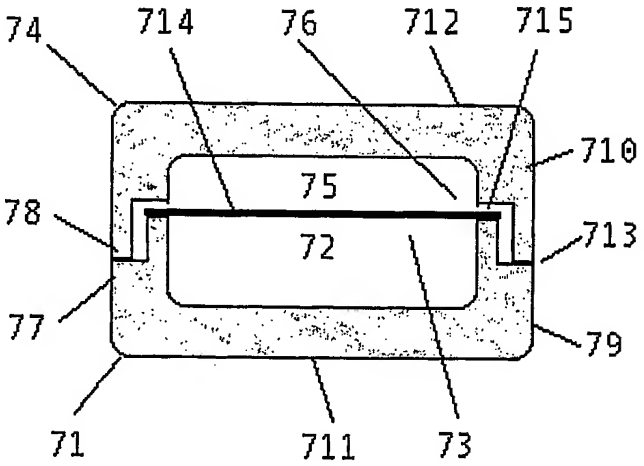

Fig 7

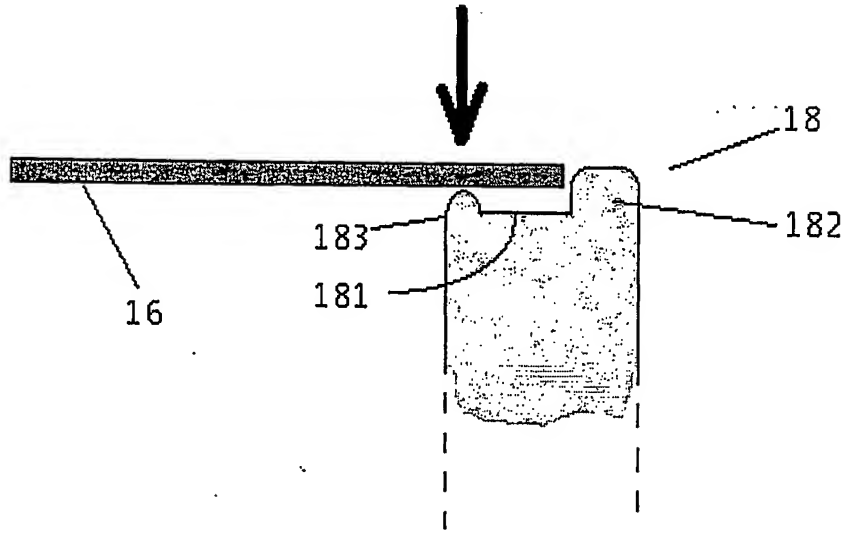

Fig 8

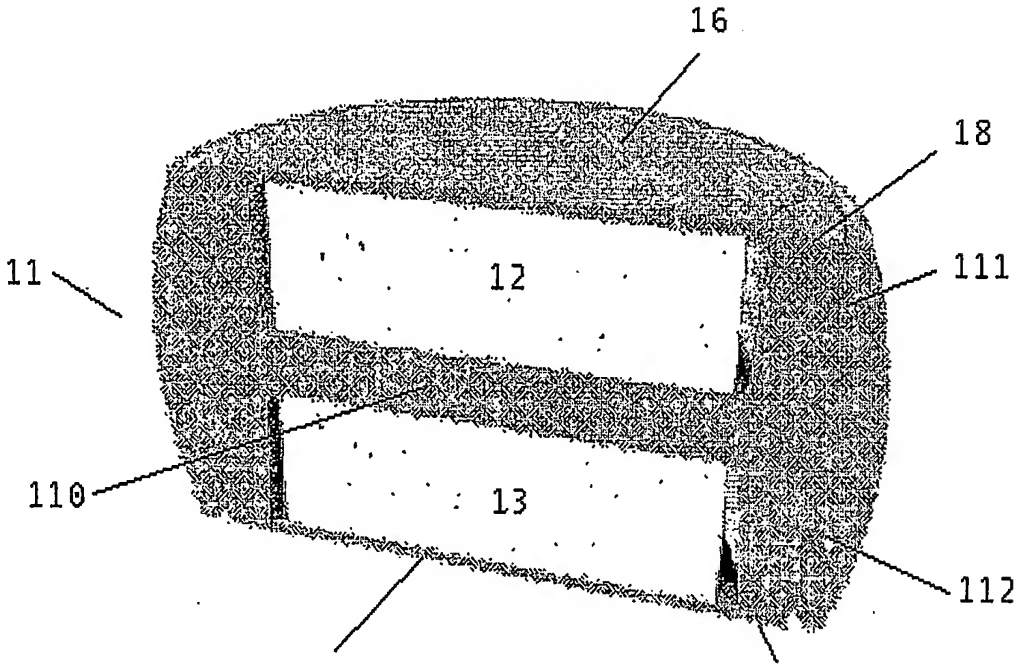

Fig 9